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Review

Current insights into pathogenesis of Parkinson's disease: Approach to mevalonate pathway and protective role of statins

Seyed Soheil Saeedi Saravi[a,b,1], Seyed Sobhan Saeedi Saravi[c,1], Katayoun Khoshbin[d], Ahmad Reza Dehpour[b,e,*]

[a] Department of Toxicology-Pharmacology, Faculty of Pharmacy, Guilan University of Medical Sciences, Rasht, Iran
[b] Department of Pharmacology, School of Medicine, Tehran University of Medical Sciences, Tehran, Iran
[c] Department of Toxicology-Pharmacology, Faculty of Pharmacy, Mazandaran University of Medical Sciences, Sari, Iran
[d] School of Medicine, Shahid Beheshti University of Medical Sciences, Tehran, Iran
[e] Experimental Medicine Research Center, School of Medicine, Tehran University of Medical Sciences, Tehran, Iran

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ABSTRACT

Although Parkinson's disease (PD) is considered as the second most common life threatening age-related neurodegenerative disorder, but the underlying mechanisms for pathogenesis of PD are remained to be fully found. However, a complex relationship between genetic and environmental predisposing factors are involved in progression of PD. Dopaminergic neuronal cell death caused by mutations and accumulation of α-synuclein in Lewy bodies and neurites was suggested as the main strategy for PD, but current studies have paid attention to the role of mevalonate pathway in incidence of neurodegenerative diseases including PD. The discovery may change the therapeutic protocols from symptomatic treatment by dopamine precursors and agonists to neurodegenerative process halting drugs. Moreover, the downstream metabolites of mevalonate pathway may be used as diagnostic biomarkers for early diagnosis of PD. Statins, as cholesterol lowering drugs, may ameliorate the enzyme complex dysfunction, a key step in the progression of the neurodegenerative disorders, oxidative stress-induced damage and neuro-inflammation. Statins exert the neuroprotective effects on striatal dopaminergic neurons through blocking the mevalonate pathway. In the present review, we have focused on the new approaches to pathogenesis of PD regarding to mevalonate pathway, in addition to the previous understood mechanisms for the disease. It tries to elucidate the novel findings about PD for the development of future diagnostic and therapeutic strategies. Moreover, we explain the controversial role of statins in improvement or progression of PD and the position of these drugs in neuroprotection in PD patients.

Contents

* Corresponding author at: Department of Pharmacology, School of Medicine, Tehran University of Medical Sciences, Tehran, Iran.
E-mail address: dehpour@yahoo.com (A.R. Dehpour).
[1] The first two authors are equally considered as leading author.

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1. Introduction

Parkinson's disease (PD), as a debilitating progressive neurodegenerative disorder, is the second most common age-related disease after Alzheimer disease [1,2]. This disease is spreading from 1% of world population over 50 years to 4% of those over 65 years [2–5]. In addition to age, incidence of the disease strongly depends on sex, genetic, ethnical and geographical factors. However, combination of a specific genetic background with a predisposing life style elevates two- to seven-fold the risk of incidence of PD [6]. PD is classified as the life-threatening diseases that shorten the duration of life, as mortality among PD patients three times more frequent than general population. It is characterized by a tetrad of permanently progressing clinical traits, bradykinesia, resting tremor, muscle rigidity, postural instability, following impaired motor function [6–8]. The patients with PD manifest both motor and nonmotor symptoms (NMS), including depression, autonomic dysfunction, sleep disturbances, sensory abnormalities, and cognitive decline [9]. The impairment of dopaminergic system following depigmentation of substantia nigra (SN) and cytoplasmic Lewy bodies (LB) are considered as the main reason for PD. Although the pathophysiological causes of motor dysfunction in PD have been well understood, the underlying mechanisms of NMS are not fully found [10–12]. As a result, there is an open avenue for the research on predisposing and possible mechanisms of pathogenesis of PD. The findings will facilitate the discovery of new therapeutic strategies for PD. Moreover, the controversial role of statins in improvement or progression of PD is discussed for clarification of their position in neuroprotective process.

2. Pathogenesis of Parkinson's disease

As a neurodegenerative disease, PD is correlated to the selective death of different types of neurons. At first step, loss of dopaminergic neurons located in the substantia nigra pars compacta (SNc) of basal nuclei, and in the tectum mesencephalicum is observed [2,6,13–15]. The decreased level of dopamine in the putamen and in the corpus striatum followed by neuronal cell death in substantia nigra leads to the emergence of motor symptoms. Clinical studies have demonstrated that typical clinical signs of PD are displayed in accordance to the death of 60–80% of dopaminergic neurons of substantia nigra pars compacta, as well as, an 80% of decrease in dopamine level in the putamen [6,14,15].

In PD, Lewy bodies and Lewy neurites, composed by proteins, fats, and polysaccharides, with radiating filaments, including α-synuclein, neurofilaments, ubiquitin, parkin, and synphilinin, aggregate in the substantia innominata [13,16]. In one hand, Lewy bodies play a neuroprotective role in PD and some other neurodegenerative diseases such as multiple systemic atrophy and Alzheimer's disease, and in healthy elderly persons [17]. On the other hand, aggregation of Lewy bodies in substantia nigra contributes to neuronal death in PD. Other features of the neurodegenerative modifications in this disease are the development of gliosis in corpus striatum and substantia nigra, leading to activation of microglia [6]. Moreover, some other potential predisposing factors contributes to pathophysiology of PD. Oxidative stress and alteration of mitochondrial function are associated with loss of dopaminergic neurons, which is caused by MPP+ (1-methyl-4-phenylpyridinium), a metabolite of mitochondrial permeability transition pore (MPTP). Disrupted catabolism of unwanted impaired or mutated multiple proteins in Lewy bodies and neurites, most notably α-synuclein, leads to cellular aggregation and neuronal death [2,18–21]. Alterations in the pro-inflammatory cytokines, including interleukin-1α (IL-1α), IL-1b and tumor necrosis factor-α (TNF-α), and inducible nitric oxide synthase (iNOS) in activated microglia are appeared. Moreover, excitotoxicity is involved in neuronal cell death caused by PD [2,22]. Although microglia activation and inflammatory response changes were both thought to be the major causes of neuronal disruption, there is body of evidences that general systemic inflammatory reactions are contributed to the pathogenesis of PD. Regarding to the widespread neuropathological picture of PD, it is assumed that degenerative processes can also be occurred in many nondopaminergic nuclei, including locus coeruleus, reticular formation of the brain stem, pedunculopontine nucleus, raphe nucleus, dorsal motor nucleus of the vagal nerve, olfactory bulbs, parasympathetic and sympathetic postganglionic neurons, basal Meynert nucleus, amygdala, hippocampus, and cerebral cortex. Degeneration of these structures by Lewy bodies leads to incidence of nonmotor clinical symptoms [23]. Furthermore, motor and nonmotor symptoms of PD are manifested, step by step, following pathological changes in dorsal motor neurons of vagal nerve, medulla oblongata, tectum mesencephalicum, and olfactory apparatus. These are resulted in olfactory disorders, constipation and sleep disturbances [24]. The typical signs of PD are developed since the dopamine level is decreased in putamen and corpus striatum, following substantia nigra and limbic system neuronal death. Ultimately, involvement of neocortex leads to loss of memory and cognitive disorders [25,26].

Despite the quoted neuropathological causes of PD, the putative role of genetic factors in the pathogenesis of PD has long been discussed. Epigenetic modifications, environmental factors and genetic mutations participate as vital players in development and regeneration of the disease [27]. Investigation of effective genetic factors on pathogenesis of PD revealed that mutations in at least 17 autosomal dominant and autosomal recessive genes are underlying the variants of the disease [28]. These gene mutations are found in α-synuclein (triplication), Parkin, ubiquitin carboxyl- terminal hydrolase L1 (UCH-L1), Parkinson disease protein 7 (DJ-1), phosphatase and tensin homolog-inducible kinase1 (PINK1), leucine-rich repeat kinase 2 (LRRK2) and glucocerebrosidase (GBA) [2].

According to the poorly known role of Lewy bodies in pathogenesis of PD, researchers have discovered an important role for α-synuclein, a major component of the radiating filaments. They mentioned that accumulation of α-synuclein protein in Lewy bodies and Lewy neurites is a pathologic hallmark of PD. As a result, dominant mutations in the α-synuclein gene (SNCA) are implicated as a distinct underlying mechanism for neurodegenerative events of PD [4,29–31].

3. New approaches to pathogenesis of PD

In the past 2 decades, brilliant advances have been obtained in finding out the mechanistic perspective of PD. Although none of current therapeutic protocols for PD have proved to obtain a convincing effect on the motor symptoms [32–36], but progressing investigations of new therapeutic strategies are performed to stop or to slow the development rate of the disease. Currently, mevalonic acid, the substrate for cholesterol and isoprenoid ubiquinone production, is located in the center stage of studies to find the pathogenic factors associated with Parkinson's disease. This phenomenon was first introduced in 1995, when Muller et al. implied a link between treatment with lovastatin, a 3-hydroxy-3-methylglutaryl Co-enzyme A (HMG-CoA) reductase (HMGCR) inhibitor, and PD in two patients [37]. They demonstrated that an inborn error of mevalonate kinase results in decreased synthesis of cholesterol and coenzyme-Q10 (Co-Q10) and, in overall, a neurological disorder [37,38]. An impairment of cholesterol synthesis is suggested to be involved in PD [39]. On the other hand, Investigations have suggested a neuroprotective effect for